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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/287,632	04/07/1999	PETER MICHAEL WATERHOUSE	021565-060	6526

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EXAMINER

ZARA, JANE J

ART UNIT	PAPER NUMBER
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1635

DATE MAILED: 11/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/287,632

Applicant(s)

WATERHOUSE ET AL.

Examiner

Jane Zara

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 September 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-10, 12, 22, 26, 40, 42-44, 46, 50, 53, 54, 56, 58 and 63-108 is/are pending in the application.
- 4a) Of the above claim(s) 1-10, 12, 40, 43, 44, 46, 50, 70-84, 88-99, 104, 105 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 22, 26, 42, 53, 54, 56, 58, 63-69, 85-87, 100-103 and 106-108 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>6-2-05</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This Office action is in response to the communication filed 9-12-05.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claims 22, 26, 42, 53, 54, 56, 58, 63-69, 85-87, 100-103, 106-108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fire et al in view of Brown et al and Lusky et al, the combination in view of Baracchini et al for the reasons of record set forth in the Office action mailed 3-11-05.

Applicant's arguments filed 9-12-05 have been fully considered but they are not persuasive. Applicants argue that the references of Fire, Brown, Lusky and Baracchini do not provide a prima facie case of obviousness and, taken together, fail to recognize the surprising results that may be obtained by the instantly claimed invention. Applicant argues that Fire does not teach an intron sequence within the context of the instantly claimed invention, that further that Brown does not teach constructs expressing dsRNA and comprising a heterologous intron arranged as presently claimed. Applicant also argues that no incentive is provided by Fire to increase the expression of a gene encoding a

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dsRNA to improve silencing, especially because Fire indicates that low concentrations of dsRNA molecules are sufficient for the purposes of dsRNA mediated gene silencing. Applicant also argues that Lusky fails to teach or suggest the arrangement of elements in the presently claimed invention and that Baracchini fails to remedy the deficiencies of the combined teachings of Fire, Brown and Lusky.

Contrary to Applicant's assertions, the instantly claimed invention would have been obvious to one of ordinary skill in the art at the time the invention was made. Fire had previously taught the general approach of gene targeting and inhibition of expression using double stranded RNA molecules. Applicants are correct that Fire teaches more efficient target gene inhibition - and hence lower concentrations necessary to achieve target gene inhibition - using dsRNA compared to previously used techniques, including antisense and triple helix approaches for inhibition. It is unclear, however, how this disclosure by Fire (e.g. of needing lower concentrations of RNAi molecules for obtaining effective levels of inhibition of target gene expression) teaches away from the historically recognized¹ and well-known advantages of including intronic sequences into recombinant expression vectors, including those encoding for dsRNA constructs.

¹ The routine incorporation of intronic sequences into recombinant expression constructs for increasing recombinant gene stability and expression has been well documented for more than 15 years. See for example the 1989 article by Xu et al that teaches increased gene expression of stably integrated and transient recombinant genes in expression constructs containing intronic sequences, compared to expression constructs lacking intronic sequences (M. Xu et al, J. Biol. Chem., Vol. 264, No. 35, pages 21,190-21,195, 1989, see esp. the abstract and introduction on p. 21,190, fig. 1 on p. 21,191, fig. 2 on p. 21,192, Table I on p. 21,193). See also C.A. Kelton et al, Molecular and Cell. Endocrin., Vol. 89, pages 141-151, 1992, esp. the abstract on p. 141, 3rd full paragraph on p. 142, bridging paragraph pp. 142-143, fig. 4 on p. 147, and first full paragraph on p. 150).

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Fire is relied upon in the instant rejection for disclosing the basic technique of gene silencing using double stranded RNA constructs. Contrary to Applicant's assertions, it would have been obvious to introduce expression constructs into plants that express double stranded RNA molecules for target gene silencing and it would have been obvious to incorporate intronic sequences into these expression constructs for enhancing the recombinant construct's stability and expression (see, for instance, col. 8-9 of Fire: "RNA may be synthesized either in vivo or in vitro. Endogenous RNA polymerase of the cell may mediate transcription in vivo... For transcription from a transgene in vivo or an expression construct, a regulatory region... may be used to transcribe the RNA strand or strands... The use and production of an expression construct are known in the art..."). Combining the seminal teachings provided by Fire, concerning dsRNA mediated inhibition of target gene expression, with the teachings of Brown concerning the routine incorporation of intronic sequences for enhancing gene expression and recombinant gene stability in plants, along with the teachings provided by Lusky concerning the routine incorporation of expression elements into recombinant expression vectors, render the instant invention obvious. One of ordinary skill in the art would have expected, therefore, that the incorporation of intronic sequences into expression vectors encoding the RNAi molecules originally taught by Fire would provide for enhanced stability of expression constructs and would provide for enhanced expression of the RNAi constructs encoded by these expression constructs. Thus, the combined teachings of Fire, Brown, Lusky, Baracchini, combined with what was well known in the art

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regarding the role of intronic sequences in providing for enhanced stability and expression of recombinant expression constructs, render the instant invention obvious to one of ordinary skill in the art at the time the invention was made.

New Rejections and Objections

Claim Objections

Claims 22, 40, 43, 44, 53, 54, 64, 66, 67, 71, 81, 82, 85, 87, 88, 92, 94, 95, 99, 100, 103, 105, 106 and 108 are objected to because of the following informalities: There is inconsistency in each of these claims in describing the extent of sequence identity encompassed by the nucleic acid constructs (e.g. compare the language in claim 22, line 8, which recites "nucleotides having between 75 and 100% sequence identity" with the language in claim 22, line 12, which recites nucleotide identity as "having between about 75% to about 100%." Replacing "75" in line 8 with -75%-- would be remedial). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22, 26, 42, 53, 54, 56, 58, 63-69, 85-87, 100-103, 106-108 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not

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described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to plant cells, plants and nucleic acid constructs comprising chimeric DNA that, when transcribed, yields RNA comprising an RNA region that forms an artificial hairpin RNA with two annealing RNA, one of which comprises a sense strand comprising at least 10, 20 or 50 consecutive nucleotides that are essentially similar to, or having between about 75% to about 100% sequence identity with, the consecutive sequences of a target gene of interest, and which chimeric DNA further comprises an annealing antisense sequence in the hairpin structure that is essentially similar to, or having between about 75% to about 100% sequence identity with, at least 10, 20 or 50 consecutive nucleotides of the complement of at least part of said target gene of interest, and which nucleic acid construct further comprises an intron sequence which is heterologous to the sense hairpin sequence, and which intron is optionally between the sense and antisense nucleotide sequences.

The specification and claims do not adequately describe the broad genus comprising chimeric DNA that, when transcribed, yield RNA comprising an RNA region that forms an artificial hairpin RNA with two annealing RNA, one of which comprises a sense strand comprising at least 10, 20 or 50 consecutive nucleotides that are *essentially similar* to, or having *between about 75% to about 100% sequence identity with*, the consecutive sequences of a target gene of interest, and which chimeric DNA further comprises an annealing antisense

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sequence in the hairpin structure that is *essentially similar* to, or having between *about 75% to about 100% sequence identity with*, at least 10, 20 or 50 consecutive nucleotides of the complement of at least part of said target gene of interest, and which nucleic acid construct further comprises an intron sequence which is heterologous to the sense hairpin sequence, and which intron is optionally between the sense and antisense nucleotide sequences. The specification teaches complementary pair constructs for reducing the phenotypic expression of a transgenic Gus gene (of approximately 1580 base pairs), and complementary pair constructs for reducing the phenotypic expression of the $\Delta 12$ desaturase target gene in *Arabidopsis* (of approximately 620 base pairs) which complementary pair constructs additionally comprise the pyruvate orthophosphate dikinase 2 intron 2 from *Flaveria trinervia* (SEQ ID NO. 7). The scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between members of this very broad is permitted (e.g. this genus embraces a myriad of sequences). The specification fails to teach or adequately describe a representative number of species in the genus such that the common attributes or characteristics concisely identifying members of the proposed genus are exemplified. And because the genus claims is so highly variant, the description provided is insufficient. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the broad genus claimed. Thus, Applicant was not in possession of the claimed genus.

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Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. 1.6(d)). The official fax telephone number for the Group is **571-273-8300**. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765**. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (571) 272-0811. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through

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Jane Zara
11-7-05

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TC1600